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Combination of active ingredients of  $\omega$ 3-fatty acid-containing oils with polyphenol-containing plant extracts and use thereof

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The present invention relates to combinations of active ingredients of  $\omega$ 3-fatty acid-containing oils with polyphenol-containing plant extracts and their use for the treatment of inflammatory and/or immunologic and metabolic diseases as well as other complaints.

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Numerous experimental and clinical studies support that  $\omega$ 3-fatty acids favourably influence the course of disease in case of chronic inflammatory and/or immunologic diseases such as atherosclerosis, coronary heart disease, rheumatoid arthritis, psoriasis and the like. Furthermore, it is reported that these fatty acids exhibit preventive and protective effects in case of disorders of the fat metabolism or diabetes and are thus suitable for the treatment of vascular and neurological disorders such as those associating these diseases. In case of a deficit of  $\omega$ 3-fatty acids in the food visual disorders and disorders of the central nervous system as well as hemorrhagic dermatitis, disturbances of growth and a delayed wound healing were observed. Since the organism of mammals is not capable of synthesizing these compounds on its own, it relies on the supply with the food.

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The observed favourable effects of  $\omega$ 3-fatty acids are explained by the fact that these substances inhibit the formation of proinflammatory prostaglandins and leucotrienes from arachidonic acid by displacing this fatty acid from its bonding in SN2-position of phospholipids of the cell membrane.

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Polyunsaturated fatty acids such as for example  $\alpha$ -linolenic acid, eicosapentaenoic acid or docosahexaenoic acid are extremely sensitive to oxidation. Therefore, the incorporation of such fatty acids or their metabolic products into cellular membranes increases the demand of the organism for antioxidants.

Epidemiological studies have revealed that the consumption of polyphenol-rich food products is associated with a reduced rate of cardiovascular diseases, cancer, osteoporosis, tumor diseases and the like. The term "polyphenols" comprises phenol carboxylic acids such as gentisinic acid, protocatechuic acid, gallic acid or 5 caffeic acid as well as flavones such as kaempferol, quercetin, myricetin, isorhamnetin, naringenin, 6-prenylnaringenin, 8-prenylnaringenin, isoxanthohumol and glycosides thereof, chalcones such as xanthohumol, isoflavones such as daidzein and genistein, anthocyanins such as pelargonidin, cyanidin, malvidin or delphinidin, tanning agents such as catechin and epicatechin, oligomers and polymers thereof 10 as well as lignans. All of these compounds are reducing agents and together with other antioxidative substances such as vitamin C and E, these compounds contribute to the protection of the body against oxidative stress. Oxidative stress designates a condition in the body, wherein the formation of oxidants and free radicals exceeds the capability of the body to inactivate these substances. As a result, 15 damages of proteins, DNA and lipids as well as damages of cell membranes and other structural elements occur. Today it is generally accepted that oxidation products are involved in the development of common diseases such as atherosclerosis, chronic inflammations, cancer or diabetes, and that they speed up the aging process. The amount of free radicals depends on the lifestyle (nutrition, smoking, 20 exercise), and is influenced by simultaneously existing diseases (such as hypercholesterolemia, diabetes). A particularly productive source of oxygen radicals are, for example, neutrophilic granulocytes which release these substances in case of 25 inflammatory reactions. Since the concentration or the activity of endogenically formed, antioxidatively acting molecules and enzymes, respectively, cannot be influenced by exogenic measures, the supply of antioxidative agents via the nutrition is of decisive importance.

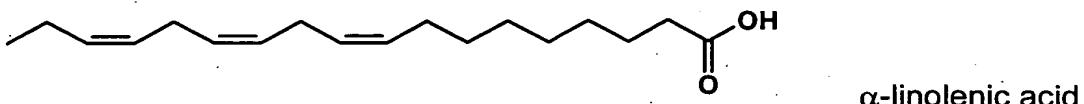
Therefore, it is the object underlying the present invention to provide agents for the prevention and treatment of inflammatory and immunologic diseases as well as tumor diseases.

30 This object is solved by a combination of active ingredients comprising at least one  $\omega$ 3-fatty acid-containing oil and at least one polyphenol-containing plant extract, wherein the combination simultaneously compensates a deficit of  $\omega$ 3-fatty acids

and antioxidative polyphenols, prevents such a deficit or satisfies increased needs for these substances in case of inflammatory and/or immunologic as well as metabolic diseases and tumor diseases.

By inhibiting the production of proinflammatory eicosanoids and neutralizing free radicals this combination of active ingredients simultaneously counteracts two important factors involved in the pathogenesis of inflammatory reactions and metabolic diseases. Additionally, this combination has the advantage that the  $\omega 3$ -fatty acids, which are sensitive to oxidation, are protected against degradation by the antioxidative effect of the polyphenols and/or vitamins both during storage and after incorporation into cell membranes.

A preferred  $\omega$ 3-fatty acid is  $\alpha$ -linolenic acid which is contained for example in an amount of about 50 – 60 % in the oil of the seeds of *perilla frutescens* (perilla oil). For this reason, perilla oil is a preferred  $\omega$ 3-fatty acid-containing oil. Further examples of suitable oils comprise borage oil, evening primrose seed oil, fish oil, currant seed oil and linseed oil.



Preferred polyphenol-containing plant extracts are extracts from *Aspalathus linearis*, *Crataegus* species, *Ginkgo biloba*, *Humulus lupulus*, *Hypericum perforatum*, *Paullinia cupana*, *Rubus fruticosus*, *Rubus idaeus*, *Tabebuia avellanedae*, *Theobroma cacao*, *Vaccinium myrtillus* and *Vitis vinifera*. However, the present invention is not limited to said plants. The polyphenol-containing plant extract preferably contains at least 15% by weight polyphenols based on the dry extract.

Combinations of active ingredients which contain one of the following combinations, are preferred: extract from *Vitis vinifera* and *perilla* seed oil, extract from *Vaccinium myrtillus* and linseed oil, extract from *Ginkgo biloba* and linseed oil, extract from *Crataegus* and borage oil, extract from *Aspalathus linearis* and borage oil, extract from *Theobroma cacao* and evening primrose seed oil, extract from *Tabebuia avellanedae* and evening primrose seed oil, extract from *Hy-*

pericum perforatum and fish oil, extract from *Humulus lupulus* and fish oil, extract from *Paullinia cupana* and currant seed oil, extract from *Rubus idaeus* and currant seed oil, extract from *Rubus fructicosus* and perilla seed oil, extract from *Aspalathus linearis* and perilla seed oil as well as extract from *Humulus lupulus* and perilla seed oil.

The extracts can be obtained in variable composition according to per se known production methods using solvents such as water, methanol, ethanol, 2-propanol, acetone and the like as well as mixtures thereof, at temperatures in the range of room temperature to 100°C under slight to vigorous mixing or by percolation within 10 minutes to 24 hours under normal pressure or increased pressure. In order to enrich the active ingredients further concentration steps such as liquid-liquid distribution using for example 1-butanol/water or ethylacetate/water, adsorption-desorption on ion exchangers, LH20, HP20 and other resins or chromatographic separations on RP18, silica gel and the like can be performed. The further processing to obtain dry extracts is carried out according to methods known per se by removing the solvent at elevated temperature and/or reduced pressure.

The combinations of active ingredients according to the present invention can be used for the treatment, for supporting the treatment or for the prophylaxis of inflammatory and/or immunologic as well as metabolic diseases and other complaints such as rheumatoid arthritis, polyarthritis, synovitis, acne, neurodermatitis, psoriasis, asthma, hay fever, atherosclerosis, coronary heart diseases or cardiac dysrhythmias, chronic intestinal diseases such as ulcerative colitis or Crohn's disease as well as polyneuropathies, retinopathies, cerebral and peripheral arterial circulatory disorders, psychiatric diseases such as depression, schizophrenia, and bipolar disorder as well as tumor diseases. However, this list of diseases, the development and course of which can be favourably influenced by the use of the combination of  $\omega$ 3-fatty acid-containing oil with polyphenol-containing plant extracts according to the present invention, is not to be considered an exhaustive list. The combination of active ingredients according to the present invention can be in the form of a dietetic food product or a pharmaceutical product.

The combinations of active ingredients according to the present invention are preferably administered within the scope of a balanced diet. Additional components such as vitamin C and/or E can be added to the combinations of active ingredients in order to compensate a deficit thereof or to satisfy an increased need therefor.

The combinations of effective ingredients according to the present invention are well-suited for being filled into capsules, because they are flowable mixtures of mostly powdery plant extracts with lipophilic plant oils. Further substances such as partially or completely hydrogenated plant oils, beeswax, lecithin, neutral oil, hardened fat and highly dispersed silicon dioxide can optionally be added to the filling material of the capsule for adjusting the consistency of the mixtures and to prevent demixing of liquid component and solid plant extract. Amphiphilic surfactants and emulsifiers such as sorbitan monooleate can be added as well to promote the dissolution of the content of the capsule released from the capsule.

15 **Examples**

The plant extract is mixed with the oil (both ingredients according to the table below) and the flowable suspension obtained is filled into capsules according to a suitable method.

**Example 1**

	Ingredients	mg/filling of the capsule
1	Extract from <i>Vitis vinifera</i>	100.0
2	Perilla seed oil	450.0

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**Example 2**

	Ingredients	mg/filling of the capsule
1	Extract from <i>Vaccinium myrtillus</i>	100.0
2	Linseed oil	450.0

**Example 3**

	Ingredients	mg/filling of the capsule
1	Extract from Ginkgo biloba	100.0
2	Linseed oil	450.0

The combinations of  $\omega 3$ -fatty acid-containing oils and polyphenol-containing plant extracts described in the examples above are characterized by inhibiting the synthesis of proinflammatory eicosanoids and neutralizing free radicals. Furthermore, these combinations have the advantage that the  $\omega 3$ -fatty acids which are sensitive to oxidation, are protected against degradation by the antioxidative effect of the polyphenols both during storing and after incorporation into cell membranes.